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Single-Nucleotide Polymorphisms in Tumor Necrosis Factor Receptor Genes

Definition of Novel Haplotypes and Racial/Ethnic Differences

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Objective. **To characterize allele frequencies of known single-nucleotide polymorphisms (SNPs) in tumor necrosis factor receptor (TNFR) genes in African Americans with rheumatoid arthritis (RA), healthy African Americans, and healthy Caucasians.**

Methods. **One *TNFRSF1B* SNP (196 G/T) that influences susceptibility to familial RA in Caucasians and 3 SNPs in the 5′ flanking region of the *TNFRSF1A* gene (−609G/T, −580A/G, and −383A/C) were genotyped in 108 African Americans with RA, 62 healthy African Americans, and 59 healthy Caucasians.**

Results. **There were no differences in *TNFRSF1A* allele frequencies between African Americans with RA and healthy African Americans. Allele frequencies were strikingly different, however, between healthy African Americans and healthy Caucasians: 0.13 versus 0.42 for −609T, 0.49 versus 0 for −580G, and 0.14 versus 0 for −383C. We identified 4 novel haplotypes defined by the 3 *TNFRSF1A* SNPs, the distribution of which was markedly different in healthy Caucasians and healthy African Americans ($P = 0.000001$ by chi-square test). The frequencies of the *TNFRSF1B* 196 genotypes were similar in African Americans with RA and healthy African Americans but differed between healthy African Americans and healthy Caucasians ($P = 0.05$).**

Conclusion. **Although we observed no associations between known TNFR SNPs or haplotypes and RA, significant racial differences were observed at both loci. Comparison of these data with other published frequencies of *TNFRSF1A* and *TNFRSF1B* genotypes according to race suggests that the distribution in African American, Caucasian, and Asian populations differs significantly. These striking racial/ethnic differences in TNFR SNP frequencies may influence the likelihood of familial RA, severe disease, or response to TNF inhibitors and may have important evolutionary implications.**

Single-nucleotide polymorphisms (SNPs) in regulatory regions of cytokine genes have important influences on gene transcription levels (1) and may influence susceptibility to and the severity of inflammatory diseases. Tumor necrosis factor (TNF) inhibitors such as etanercept, a TNF receptor II (TNFRII):Fc IgG1 fusion protein, and infliximab, a chimeric monoclonal anti-TNF antibody, are effective in the treatment of RA, underscoring the relevance of TNF in the pathogenesis of the disease. Genetic variations in the TNF locus, including microsatellites (2–4), and SNPs located at −376, −308, −238, −163, +70, and +488 (intron 1) relative to the transcription start site (5), have been analyzed for their role in susceptibility to or the severity of RA. Polymorphic variants in TNFR genes have been touted as potentially important in RA, but racial and ethnic differences in allele frequencies have not yet been fully explored.

There are 2 major TNF receptors: TNFRI (CD120a, the 55/60-kd receptor), which is encoded by

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the *TNFRSF1A* gene, and TNFRII (CD120b, the 75/80-kd receptor), which is encoded by the *TNFRSF1B* gene. *TNFRSF1A* is expressed in all nucleated cells, particularly those susceptible to the cytotoxic action of TNF, and *TNFRSF1B* is expressed predominantly in cells of myeloid origin, particularly stimulated T and B lymphocytes.

The *TNFRSF1A* gene is located on chromosome 12p13 and contains 10 exons. An 809-bp region in the 5′ flanking region of the gene appears to be active in gene transcription (6). The *TNFRSF1A* promoter region resembles that of housekeeping genes, in that transcription has multiple start points, and there are no canonical TATA or CAAT box motifs. Several genetic variants in the human *TNFRSF1A* gene (7–9) have been identified, including 3 SNPs in the 5′ promoter region, but their effects on transcription or protein function are unknown. Missense mutations in the coding region of the *TNFRSF1A* gene have been identified in families affected by autoinflammatory syndromes characterized by fever and arthralgias (10).

The *TNFRSF1B* gene is located on chromosome 1p36, consists of 10 exons (11), and contains a variety of microsatellite markers and SNPs. A genome scan performed on a large cohort of sibling pairs has suggested linkage of susceptibility to RA to markers close to the *TNFRSF1B* locus (12). Three genetic variants coding for different protein sequences have been reported in exon 4 (143 C/G), exon 6 (196 T/G), and exon 9 (365 A/C) (11). The *TNFRSF1B* codon 196 T/G SNP encodes an amino acid change (methionine to arginine), but the functional consequences of the amino acid change are incompletely understood. Caucasian patients with RA are significantly more likely to be positive for the G allele and GG genotype than are Caucasian controls, but this association appears to be confined to those with a family history of RA (13). The *TNFRSF1B* codon 196 SNP was also studied in 545 Japanese patients with RA and 265 Japanese controls, but no significant association between the polymorphism and susceptibility to RA was observed (14).

The present study sought to test the hypothesis that there may be racial or ethnic differences in the frequencies of individual TNFR SNPs or haplotypes, which may provide important markers of disease susceptibility, disease severity, or response to treatment with TNF inhibitors.

PATIENTS AND METHODS

Patients and controls. This analysis included 229 individuals: 108 African-American patients with RA from the Grady African-American Rheumatoid Arthritis (GAARA) cohort (15), 62 healthy African Americans, and 59 healthy Caucasians. The GAARA patient population is derived from a group of patients with RA followed up in rheumatology clinics at Grady Memorial Hospital. A comprehensive set of sociodemographic, clinical, radiologic, and laboratory data has been collected. Fifty-two unrelated healthy African-American blood donors were recruited as controls through the Grady Memorial Hospital, the Atlanta Veterans Administration Medical Center, and the blood donor program of the Scientific Resources Program, National Center for Infectious Diseases (NCID), Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. Other controls included 10 healthy African Americans and 10 healthy Caucasians from Birmingham and 49 healthy Caucasians from the blood donor program of the Scientific Resources Program, NCID, CDC, Atlanta, Georgia.

GAARA participants recorded their country of birth and a race and ethnicity history for themselves, their parents, and their grandparents. African Americans were defined as persons who recorded their race as black and who were born in the US or its territories. All GAARA patients and controls were from the southeastern US. For the GAARA patients included in this study, the mean ± SD age at onset of RA was 43.7 ± 13.4 years, and the mean ± SD disease duration at the time of study entry was 13.9 ± 11.6 years. Of the 108 GAARA patients, 84.3% were women, and 74.3% were rheumatoid factor positive. Among the GAARA patients, 34.3% were HLA–DR4–positive, compared with 11.5% of the GAARA controls.

Genotyping methods. *TNFRSF1A SNPs.* To allow simultaneous determination of genotypes at the −609, −580, and −383 SNPs, a 500-bp fragment of the 5′ flanking region of the *TNFRSF1A* gene was amplified from genomic DNA by polymerase chain reaction (PCR). Each PCR reaction used 20–50 ng of genomic DNA and included 200 μM of deoxyribonucleoside triphosphate, 1.5 m*M* of $MgCl_2$, 400 n*M* of each primer, and 2.5–10 units of *Taq* polymerase in standard PCR buffer. The following PCR primers were used: 5′-TCGGACGCTTATCTATATCTCTCC-3′ (sense), and reverse 5′-TCTGAGAAAATTAAAGCAGAGAGGA-3′ (antisense). PCR was performed under the following conditions: 95°C for 5 minutes, followed by 35 cycles of 95°C for 1 minute, 56°C for 30 seconds, 72°C for 1 minute, then a final extension step of 7–10 minutes at 72°C. PCR products were analyzed by electrophoresis on 2% agarose gel, followed by excision of bands from the gel and purification using the Qiaquick gel extraction kit (Qiagen, Chatsworth, CA). Direct cycle sequencing of the amplified product was performed on an ABI 377 automated sequencer using the BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA), which is optimized for heterozygote detection. Sequencing was performed from each strand, using the same 2 primers used in the PCR reaction, in separate sequencing reactions.

Haplotypes were deduced for individuals who were homozygous at all 3 SNPs or who were heterozygous at only 1 site. For each individual who was heterozygous at more than 1 site, genomic DNA (amplified as described above) was cloned into the pCRII plasmid vector using the TA cloning kit (Invitrogen, San Diego, CA), and individual clones were isolated and sequenced to define haplotypes.

TNFRSF1B SNPs. Because of the reported importance of the *TNFRSF1B* 196 T/G SNP in exon 6, we initially focused on it. The following PCR primers were used for amplification: 5′-ACTCTCCTATCCTGCCTGCT-3′ (sense), and 5′-TTCTGGAGTTGGCTGCGTGT-3′ (antisense). A total of 20–50 ng of genomic DNA was used, along with 200 μM of dNTP, 1.5 mM of $MgCl_2$, 400 nM of primers, and 2.5–10 units of *Taq* polymerase in standard PCR buffer. PCR conditions were as follows: 96°C for 10 minutes, followed by 35 cycles of 96°C for 30 seconds, 60°C for 30 seconds, and 72°C for 1 minute, then an additional 10-minute extension step at 72°C. PCR products were digested with *Nla* III (New England Biolabs, Beverly, MA) as described by Barton et al (13), then subjected to agarose gel electrophoresis. Presence of the G allele produces a 242-bp band, while presence of the T allele produces a 134-bp band and a 113-bp band.

In an attempt to define SNP haplotypes in the *TNFRSF1B* gene, we first genotyped 10 healthy Caucasians and 10 healthy African Americans for polymorphic variants reported in exon 4 (143 C/G) and exon 9 (365 A/C) (11). For the 143 G/C SNP, the sense primer was 5′-CTCTAGACCAGGTGGAAACTCAAG-3′, and the antisense primer was 5′-GTCCCCAAGGACCTGAGC-3′. For the 365 A/C SNP, the sense primer was 5′-CTCACTTGCCTGCCGATAA-3′, and the antisense primer was 5′-GTGTGCTCCCACCTCTTACCT-3′. PCR was performed using standard PCR buffer with 200 μM of dNTP, 1.5 mM of $MgCl_2$, 400 nM of primers, 20–50 ng of genomic DNA, and 2.5–10 units of *Taq* polymerase. PCR conditions were similar to those described for the *TNFRSF1B* 196 SNP, with the exception that an annealing temperature of 56°C was used. PCR products were purified and sequenced as described above for *TNFRSF1A*.

Statistical analysis. Comparisons between patients with RA and healthy controls within the same racial or ethnic group and between healthy individuals of different racial or ethnic groups were performed using the chi-square test or Fisher's exact test, 2-tailed as appropriate.

RESULTS

TNFRSF1A. There were no significant differences in allele frequencies of SNPs in the *TNFRSF1A* gene at positions −609, −580, and −383 SNPs between African Americans with RA and African American controls (Table 1), suggesting that this locus has no influence on susceptibility to RA in African Americans. There were, however, striking differences between healthy African Americans and healthy Caucasians. For example, the −580 G allele was not observed in any of the 59 Caucasians, but the frequency in healthy African Americans was 0.49 ($P < 0.00000001$). In contrast, the −609 T SNP was more common in Caucasian controls than in African American controls (0.42 versus 0.13, $P < 0.000001$). The −383 C allele was not demonstrated in any Caucasians, but the frequency in African American controls was 0.14 ($P < 0.000001$).

Table 1. Frequencies of genotypes of single-nucleotide polymorphisms (SNPs) in the *TNFRSF1A* gene*

	African Americans with RA (n = 108)	Healthy African Americans (n = 62)	Healthy Caucasians (n = 59)
SNP position			
−609 G	194 (0.90)	108 (0.87)†	68 (0.58)
−609 T	22 (0.10)	16 (0.13)	50 (0.42)
−580 A	101 (0.47)	63 (0.51)‡	118 (1.0)
−580 G	115 (0.53)	61 (0.49)	0
−383 A	196 (0.91)	107 (0.86)§	118 (1.0)
−383 C	20 (0.09)	17 (0.14)	0
Haplotypes −609/−580/−383			
G/G/A	96 (0.44)	47 (0.38)¶	0
G/A/A	79 (0.37)	45 (0.36)	68 (0.58)
G/G/C	19 (0.09)	17 (0.14)	0
T/A/A	22 (0.10)	15 (0.12)	50 (0.42)

* Allele frequencies of SNPs at positions −609, −580, and −383 are relative to the transcription start site. RA = rheumatoid arthritis. Values are the no. (frequency).
† $P < 0.000001$ versus healthy Caucasians, by chi-square test.
‡ $P < 0.00000001$ versus healthy Caucasians, by chi-square test.
§ $P = 0.000006$ versus healthy Caucasians, by chi-square test.
¶ $P = 0.000001$ versus healthy Caucasians, by chi-square test.

We were able to deduce 4 haplotypes of the *TNFRSF1A* 5′ flanking region, because at least 1 individual was homozygous for each allele of each of the 3 SNPs. No additional haplotypes were determined by the sequence analysis of cloned PCR products. There were no differences in *TNFRSF1A* allele frequencies, haplotype distributions, or haplotype combinations between African Americans with RA and African American controls (Table 1 and Figure 1). There were striking differences, however, in the haplotype frequencies and

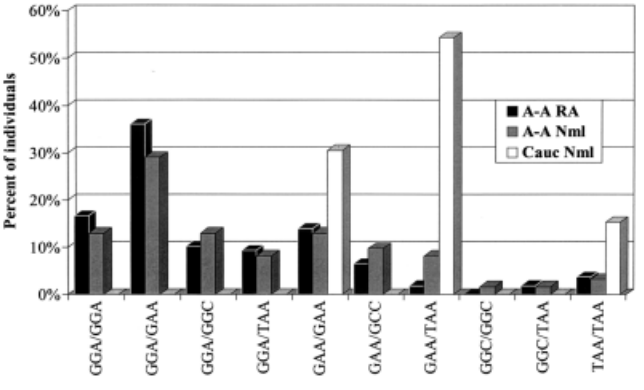

Figure 1. Distribution of tumor necrosis factor receptor I haplotypes. The difference in haplotype combinations between African American controls (A-A Nml) and Caucasian controls (Cauc Nml) was highly statistically significant ($P = 0.000001$, by chi-square test). RA = rheumatoid arthritis.

Table 2. Frequencies of genotypes of the *TNFRSF1B* 196 single-nucleotide polymorphism*

	Present study			Barton et al (13)		Shibue et al (14)	
	African Americans with RA (n = 108)	Healthy African Americans (n = 62)	Healthy Caucasians (n = 59)	Caucasians with RA (n = 597)	Healthy Caucasians (n = 137)	Japanese with RA (n = 545)	Healthy Japanese (n = 265)
Allele							
196 T	173 (0.80)†	103 (0.83)	86 (0.73)‡	803 (0.67)	204 (0.74)	932 (0.86)	470 (0.89)
196 G	43 (0.20)	21 (0.17)	32 (0.27)	391 (0.33)	70 (0.26)	158 (0.14)	60 (0.11)
196 genotype							
TT	70 (0.65)§	41 (0.67)¶	32 (0.54)	272 (0.46)	74 (0.54)	404 (0.74)	208 (0.79)
TG	33 (0.31)§	21 (0.33)¶	22 (0.37)	259 (0.43)	56 (0.41)	124 (0.23)	54 (0.20)
GG	5 (0.05)§	0¶	5 (0.08)	66 (0.11)	7 (0.05)	17 (0.03)	3 (0.01)

* Values are the no. (frequency).
† $P = 0.0002$ versus Caucasians with RA, by chi-square test.
‡ $P = 0.00002$ versus healthy Japanese, by chi-square test.
§ $P = 0.0008$ versus Caucasians with RA, by chi-square test.
¶ $P = 0.05$ versus healthy Caucasians, by chi-square test.

haplotype combinations observed in African Americans and those observed in Caucasians ($P < 0.000001$) (Figure 1), due to the differences in allele frequencies.

TNFRSF1B. The frequencies of the *TNFRSF1B* 196 G allele and the GG genotype were slightly higher in African Americans with RA than in African American controls (0.20 versus 0.17 and 0.05 versus 0, respectively) (Table 2), but these differences were not statistically significant. In African American controls, the 196 G allele frequency was 0.17, which was lower than (but not statistically different from) that in Caucasian controls (0.27). There was no difference in the distribution of TT, TG, and GG genotypes in African Americans with RA and African American controls, but genotype distributions were significantly different ($P = 0.05$) between healthy Caucasians (0.54, 0.37, and 0.08, respectively) and healthy African Americans (0.67, 0.33, and 0, respectively).

Analysis of 10 healthy Caucasians and 10 healthy African Americans indicated the relative rarity of the *TNFRSF1B* 143 C and 365 A alleles in both racial groups: all 20 subjects were homozygous for GG at the 143 C/G SNP, while all 18 individuals who were successfully genotyped at the 365 SNP (9 African Americans and 9 Caucasians) were CC homozygotes. Thus, no other individuals in this study were genotyped at these 2 SNPs, because the allele frequencies were likely to be too low to be useful in delineating haplotypes.

DISCUSSION

Racial differences in the distribution of genes of the major histocompatibility complex (MHC) such as the HLA classes I and II and TNF loci have been well documented. Although our study demonstrated no evidence for associations of any of the *TNFRSF1A* or *TNFRSF1B* SNPs or haplotypes with RA in African Americans, we documented significant racial diversity in these genotypes. Our data provide evidence that there are significant racial differences in the distribution of genes outside the MHC that code for important immune system molecules. These findings emphasize the importance of determining background gene frequencies in individual racial groups as a prelude to analyzing gene–disease associations in different populations, and for studies of evolutionary divergence.

We have shown significant differences between healthy African Americans and healthy Caucasians in the distribution of 3 SNPs in the *TNFRSF1A* 5′ flanking region, although the number of Caucasian controls in this study was relatively small (n = 62). The rarity of the *TNFRSF1A* −383 C allele in our Caucasian population (0 of 118 alleles) is corroborated by 2 other studies of healthy Caucasians. In a study from the UK, only one −383 C allele was observed among 152 individuals (allele frequency 0.003) (9). Similarly, only one −383 C allele was reported among 103 healthy Caucasians from Sweden (allele frequency 0.005) (16). The frequencies of the 3 *TNFRSF1A* alleles in our Caucasian control subjects were similar to those reported in 100 patients from Olmstead County, Minnesota (who, presumably, were mostly Caucasian) with multiple sclerosis: 0.65 for −609 G, 0.36 for −609 T, 0.99 for −580 A, 0.01 for −580 G, 0.99 for −383 A, and 0.01 for −383 C (8). The frequency of the −383 C allele in Chinese individuals from Hong Kong was reported to be 0.07 (16), which is intermediate between the frequencies in Caucasians and African

Americans. Together, these data suggest significant global racial diversity in the distribution of *TNFRSF1A* genotypes. Interestingly, the distribution of *TNFRSF1A* haplotypes appears to be much more heterogeneous among African Americans than among Caucasians (Figure 1). This could reflect evolutionary divergence, as is observed for the MHC, or could be attributable to racial admixture.

It is unknown whether the 3 *TNFRSF1A* SNPs influence gene transcription, but they are located in a region purported to have promoter and inhibitor functions (6). Even in the absence of a biologic effect, these SNPs may be part of an extended haplotype in which interactions of multiple SNPs can affect biologic activity and response to medication, as is the case with SNPs in the human β_2-adrenergic receptor gene. In that gene, 13 SNPs form 12 haplotypes with marked divergence in their distribution in different racial and ethnic groups (17). In patients with asthma, the bronchodilator response to a β agonist correlated with haplotype combination but not with any individual SNPs. Such may be the case with *TNFRSF1A*, in which the level of surface expression of *TNFRSF1A* on target cells may influence their activation by TNF or lymphotoxin α, both of which can bind to *TNFRSF1A*.

No association between the *TNFRSF1B* 196G allele and RA was observed in African Americans in our study. This is similar to the lack of association between this allele and RA observed in Japanese populations (14). Although an association of the 196 allele with RA was observed in Caucasians in the UK, this association was confined to patients with a family history of RA (13). Among the GAARA patients, we saw no significant association between *TNFRSF1B* 196 genotype and family history of RA (data not shown).

Significant racial differences in 196 G allele and genotype distributions appear to exist, as summarized in Table 2. The frequency of the 196 G allele is significantly higher in healthy Caucasian subjects than in the healthy Japanese subjects reported by Shibue et al (14) (0.27 versus 0.11; $P = 0.00002$). The frequency of this allele in healthy African Americans in our study (0.17) was intermediate between those reported in healthy Caucasian and Japanese populations. There was also a trend toward a difference between the distribution of TT, TG, and GG genotypes in healthy African Americans (0.67, 0.33, and 0, respectively) and healthy Japanese subjects (0.79, 0.20, and 0.01, respectively), but the difference was not statistically significant ($P = 0.058$ by chi-square test).

Within populations of patients with RA, significant racial differences are also observed. This may reflect the differences in background frequencies between the races. For example, the frequency of the 196 G allele in African American patients with RA in our study (0.20) is reduced compared with that in the Caucasian patients with RA from the UK studied by Barton et al (13) (0.33; $P = 0.0002$), and this frequency is intermediate between that observed in Japanese patients with RA (0.14) (14) and Caucasians with RA. As would be expected from the differences in allele frequencies, there was a significant difference in the distribution of patients with the TT, TG, and GG genotypes among African Americans with RA (0.65, 0.31, and 0.05, respectively) and Caucasians with RA (0.46, 0.43, and 0.11, respectively) ($P = 0.0008$ by chi-square test).

The *TNFRSF1B* 196G allele has been implicated in systemic lupus erythematosus and appears to be in linkage disequilibrium with a 56G allele (18). Functional analysis of the 196G allele suggests it is associated with increased production of interleukin-6 and increased cytotoxicity compared with the 196T allele, despite similar binding affinities for TNF (18). The *TNFRSF1B* 196 SNP lies in the extracellular domain; therefore, we speculate that this SNP may impact binding of TNFα-converting enzyme, which is the molecular defect causing impaired receptor shedding in autoinflammatory conditions such as familial periodic fever syndromes, now referred to as TRAPS (TNFR-associated periodic syndromes) (10).

In conclusion, we have demonstrated marked differences in the distribution of TNF receptor SNPs and haplotypes among individuals of different races and ethnicities. Whether these genetic differences influence disease severity or response to treatment (particularly to TNF inhibitors) is unclear and will be the focus of future investigation.

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